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Increased respiratory neural drive and work of breathing in exercise-induced laryngeal obstruction

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ABSTRACT

Rationale

Exercise induced laryngeal obstruction (EILO), a phenomenon in which the larynx closes inappropriately during physical activity, is a prevalent cause of exertional dyspnea in young individuals. The physiological ventilatory impact of EILO and its relationship to dyspnea are poorly understood.

Objectives

To evaluate exercise related changes in laryngeal aperture on ventilation, pulmonary mechanics and respiratory neural drive.

Methods

We prospectively evaluated 12 subjects (six with EILO and six healthy age- and gender-matched controls). Subjects underwent baseline spirometry and a symptom-limited incremental exercise test with simultaneous and synchronized recording of endoscopic video, gastric-, esophageal- and transdiaphragmatic pressures, diaphragm electromyography and respiratory airflow.

Results

The EILO and control groups had similar peak work rates and minute ventilation ($\dot{V}_E$) (work rate: 227±35 vs. 237±35W; $\dot{V}_E$: 103±20 vs. 98±23 L/min; $p>0.05$). At submaximal work rates (140–240W) subjects with EILO demonstrated increased work of breathing ($p<0.05$) and respiratory neural drive ($p<0.05$), developing in close temporal association with onset of endoscopic evidence of laryngeal closure ($p<0.05$). Unexpectedly, a ventilatory increase ($p<0.05$), driven by augmented tidal volume ($p<0.05$), was seen in subjects with EILO, before

the onset of laryngeal closure; there were however no differences in dyspnea intensity between groups.

Conclusion

Using simultaneous measurements of respiratory mechanics and diaphragm electromyography with endoscopic video we demonstrate, for the first time, increased work of breathing and respiratory neural drive in association with the development of EILO. Future detailed investigations are now needed to understand the role of upper airway closure in causing exertional dyspnea and exercise limitation.

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NEW & NOTEWORTHY

Exercise-induced laryngeal obstruction is a prevalent cause of exertional dyspnea in young individuals; yet, how laryngeal closure affects breathing is unknown. In this study we synchronized endoscopic video with respiratory physiological measurements; thus providing the first detailed commensurate assessment of respiratory mechanics and neural drive in relation to laryngeal closure. Laryngeal closure was associated with increased work of breathing and respiratory neural drive preceded by an augmented tidal volume and a rise in minute ventilation.

INTRODUCTION

Exercise induced laryngeal obstruction (EILO), a phenomenon in which the larynx closes inappropriately during physical activity, is now recognized to be an important and prevalent cause of exertional dyspnea (4, 23). Specifically EILO is reported to be present in approximately 5-10% of all adolescents (5, 13) and is a key differential diagnosis for unexplained dyspnea in athletic individuals (23).

The development of EILO is associated with high exercise intensity (25) and is thus best studied using continuous laryngoscopy during exercise (CLE) (11). This approach can reveal the development of any tendency to paradoxical laryngeal closure on inspiration, occurring at either the glottic (i.e. adduction of the vocal folds and often termed exercise associated vocal cord dysfunction [VCD]) and/or the supra-glottic level (i.e. arytenoids and aryepiglottic folds partially or fully obstruct the laryngeal inlet) (19); however, the physiological mechanisms underpinning the regulation of laryngeal function and the ventilatory response to EILO remain poorly understood.

In respiratory disorders it is now recognized that the intensity of exertional dyspnea relates to heightened respiratory neural drive (RND) to the diaphragm (9, 16). The latter can be assessed by quantifying the electromyogram of the crural diaphragm (EMGdi), expressed as a percentage of volitional maximum (EMGdi/EMGdi,max) (9, 14, 15, 30) and this can be best contextualized by simultaneous measurement of the mechanical/muscular response of the respiratory system, in relation to external work and measures of ventilation (26). Indeed, this approach has significantly progressed our understanding of the mechanisms underpinning respiratory limitation and exertional dyspnea in respiratory disease (9, 16).

It is believed that EILO is primarily a maladaptive process and thus it may be hypothesized that it would be associated with heightened and inappropriate respiratory loading and ventilatory work, as a consequence of augmented inspiratory resistance. This association has however not be studied and indeed in contrast to this we have previously shown that in obstructive lung disease (i.e. augmented *expiratory* resistance) exercise-associated laryngeal closure may actually be adaptive and thus beneficial for exercise pulmonary dynamics (2). It is currently unknown whether laryngeal closure is associated with changes in respiratory mechanics or RND or indeed how this relates to the development of exertional dyspnea.

The aim of the present study was therefore to conduct a pilot study to evaluate the time course of changes in laryngeal closure, breathing pattern, pulmonary mechanics and RND to better understand the underlying physiological mechanisms and ventilatory response of laryngeal closure and its relation to exertional dyspnea. We hypothesized that the development of EILO would be associated with increased inspiratory work of breathing and RND.

METHODS

Subjects

We prospectively evaluated 12 subjects; six with EILO, defined as glottic or supraglottic EILO of at least moderate severity based on accepted criteria (5) selected from a clinical database of subjects with EILO aged >18 years and six healthy age- and gender-matched control subjects. All subjects were non-smokers who participated in regular physical activity. Two subjects in the EILO group also had well-controlled mild asthma and both took their inhaled medications, as prescribed, prior to assessment. All patients and two controls had previously undergone exercise laryngoscopy testing and were thus familiar with the procedure.

Study Design

Subjects attended on one occasion for detailed physiological assessment, including spirometry, measurement of maximal sniff and mouth inspiratory pressure (MIP) and a symptom-limited incremental CLE test, with simultaneous and continuous measurement of diaphragm electromyography (EMGdi), respiratory pressures (gastric, esophageal and transdiaphragmatic) and respiratory airflow. Subjects refrained from a heavy meal, alcohol and vigorous exercise on the day of testing.

The study received ethical approval from the NRES Committee London-Dulwich (ref. no. 15/LO/0047) and all subjects provided written consent.

Procedures

Anthropometric data were recorded and baseline spirometry was measured (Jaeger, CareFusion, Heidelberg, Germany) (22).

An incremental (20W/min) exercise test was then conducted on an electronically braked cycle ergometer to volitional exhaustion (Ergoselect VIAsprint 150 P, ergoline GmbH, Bitz, Germany) with continuous measurement of respiratory airflow using a pneumotachograph (Hans Rudolph Inc., Shawnee, KS, USA), calculating volume changes from the integral of the flow signal. Subjects rated dyspnea intensity and leg discomfort at each incremental exercise stage on the modified Borg scale (3) and performed inspiratory capacity (IC) maneuvers at rest and at the end of each workload.

Diaphragm Electromyography and Respiratory Pressure Measurements

Esophageal pressure (Pes), gastric pressure (Pga), and EMGdi were measured synchronously (Figure 1a) using a combined multipair electrode-balloon catheter system (Guanzhou Yinghui Med Eq Co., China), inserted per-nasally and analyzed as previously described (15, 17). A minimal quantity (i.e. <1 mL) of local anaesthetic gel (2.0g Lidocaine Hydrochloride / 0.25g Chlorhexidine Gluconate) was applied to the tip of the EMG/pressure catheter. The raw EMGdi signal was sampled at 4000 Hz (PowerLab; ADInstruments, Sydney, Australia), band-pass filtered between 20-1000 Hz (Bioamplifier model 08-GL; Guanzhou Yinghui Med Eq Co., China) and converted to a root mean square (RMS). Maximal EMGdi (EMGdi,max) was determined as the largest EMGdi RMS from any IC maneuver performed at rest or exercise. EMGdi/EMGdi,max was used as an index of inspiratory diaphragm neural drive (8, 10).

Integrated continuous laryngoscopy during exercise

Laryngoscopic video was acquired continuously during exercise. In brief a flexible laryngoscope (ENF-VQ, Olympus, Tokyo, Japan) was placed in situ with the controller secured on a headpiece. The video was then synchronized with pressure-, EMG- and flow signals (Figure 1b) via a MacBook Pro (Apple Inc., Cupertino, CA, USA) and LabChart 7 data acquisition software (ADInstruments, Sydney, Australia) via an analog-to-digital converter

(BlackMagic Design, Port Melbourne, Australia) feeding to a video capture device (SDI2USB 3.0, Epiphan Video, Ottawa, Canada) (Video E1 in the online supplement).

Data analysis

The final 30 seconds of the resting phase and each exercise workload were analyzed, having disregarded any irregular breaths (e.g. swallow or cough). Laryngeal closure was described using a sum-score, i.e. 0–3 points (corresponding to no, mild, moderate or severe closure) at both the glottic and supraglottic level based on changes in anatomical appearance (19). The highest score observed during a given workload was recorded. Work of breathing (inspiratory resistive, inspiratory elastic, expiratory and total) was calculated for each breath from pressure-volume loops (6) and averaged for each workload (Figure 1c) after adjusting ambient temperature (24°C), pressure (101,3 kPa), relative humidity (50%) and volume drift.

Trans-diaphragmatic pressure (Pdi) was calculated as the difference between Pes and Pga. Maximal Pdi (Pdi,max) and Pes (Pes,max) were determined as the highest value in sniff, MIP or IC maneuvers. Tidal Pes swings (Pes,tidal) were defined as the amplitude between the maximum expiratory value and minimum inspiratory value for each respiratory cycle. The Pdi tidal swing was defined as the amplitude of the Pdi waveform during tidal breathing. Data points of zero flow, EI and EE for Pes and Pga were collected. Dynamic compliance (C_{dyn}) was calculated as the change in lung volume divided by change in Pes between EE and EI (31). Total airways resistance was calculated as the difference in Pes divided by the difference in flow at inspiratory mid-volume and expiratory iso-volume ($\Delta Pes/\Delta flow$). Tension time index of the diaphragm (TTIdi) and the inspiratory muscles (TTIes) were calculated as the product of tidal Pdi and Pes and the ratio of inspiration time to breath cycle (20, 28).

Statistical Analysis

Differences in characteristics between the EILO and control group were compared using Mann-Whitney U tests for continuous data and Fisher's Exact for categorical data. Group differences for repeated measurements were analyzed by means of a linear mixed model with random intercept and slope. In this pilot study, no power calculation was performed. Statistical analysis was performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS 24.0 (SPSS Inc., Chicago, IL, USA) and a *p*-value of <0.05 was considered significant.

RESULTS

By design, EILO and control groups were matched for age, sex, height and weight (Table 1). In addition, as expected laryngoscopic video of the EILO group revealed marked laryngeal obstruction (i.e. moderate or severe grade) in all subjects, arising from a median (range) workload of 180W (120-240W) (Figure 2a).

Resting pulmonary function

The EILO and control groups had normal and comparable resting spirometric indices (Table 1). However, in comparison with controls, subjects with EILO had a greater resting IC than controls (131% predicted vs. 101% predicted, respectively, $p=0.02$; Table 1) and a trend towards a lower peak inspiratory flow (PIF median: 6.34 vs. 8.01 L/s, $p=0.08$; Table 1). There were no differences in Pes and Pdi pressure measurements in sniff, IC and MIP maneuvers between groups at rest (Table 1).

Exercise response and ventilatory pattern

The EILO and control groups had a similar peak power output and minute ventilation (power: 227±35 vs. 237±35 watts; $\dot{V}_E$: 103±20 and 98±23 L/min, respectively; $p>0.05$; all numbers mean±SD), however at submaximal work rates (140-240 watts), and before the onset of laryngeal closure, the EILO group had a greater $\dot{V}_E$ ($p<0.05$; Figure 2b). This difference was attributable to a greater tidal volume (V_T) (Figure 2c), with no difference in breathing frequency (Figure 2d), peak inspiratory flow, or peak inspiratory flow or inspiratory flow at mid-volume (Figure 3d) observed between groups. There was however a trend towards disproportionate hyperpnoea in the EILO group at workloads of ≥180W.

In keeping with the data at rest, the EILO group had a greater IC at lower work rates compared with controls (Figure 2e), but there was no difference in inspiratory duty cycle (T_i/T_{tot}) between the two groups (Figure 2f).

Ventilatory mechanics and respiratory neural drive

EMGdi/EMGdi,max was significantly higher from a submaximal work rate (mean 67% of peak work rate) to peak exercise in the EILO group compared to control group (Figure 3a). This coincided with laryngoscopic evidence of the onset of clinically significant (i.e. moderate or severe) laryngeal narrowing. Indices of respiratory effort (Pes/Pes,max) and work of breathing were greater in EILO subjects at higher intensity work rates, when compared to controls and this was explained by increased inspiratory resistive work (Figure 3c) and to some extent expiratory work of breathing and total airway resistance (Figure 3e), with no changes in inspiratory elastic work. The EILO group had a greater dynamic compliance (C_{dyn}) compared controls at rest and during unloaded exercise (Figure 3f). The groups had similar EMGdi for any given $\dot{V}_E$. Taken together, the mechanical load and metabolic cost of breathing (tension

time index for Pes and Pdi [TTIes, TTIdi] and pressure time products for Pes and Pdi [PTPes, PTPdi]) were greater in EILO subjects at higher intensity work rates, compared with controls whilst there were no differences in markers of expiratory muscle recruitment (i.e. end-expiratory Pes and pressure time product for Pga; data not shown).

Dyspnea and leg fatigue responses to exercise

Dyspnea intensity rating was slightly, but not significantly ($p>0.05$), higher in EILO than controls for a given submaximal exercise work rates (Figure 4a). At high exercise intensity, EILO and control groups had evidence of a similar plateau in reported dyspnea, despite increased RND and $\dot{V}_E$ levels in the EILO group (Figure 4b–c). There were no differences in leg fatigue between the groups at any work rate (e.g. 180W = 3.2±1.0 vs. 3.5±1.5 and 240W = 5±0 vs. 4.8±1.7, EILO vs. Controls, respectively).

DISCUSSION

The development of laryngeal closure on exertion is associated with expected physiological mechanisms (i.e. increased work of breathing, inspiratory resistance and heightened respiratory neural drive). These abnormalities developed in close temporal association with video evidence of laryngeal closure and thus delineate the physiological impact of this closure and provide a correlate for the typical symptoms reported by individuals with EILO. Surprisingly, an increase in minute ventilation driven by a higher V_T was seen in subjects with EILO at lower work rates and before the onset of laryngeal closure. Taken together the findings provide the first detailed physiological insight regarding the impact of laryngeal closure on ventilatory mechanics and the associated sequelae for respiratory load and associated work of breathing.

Laryngeal obstruction, work of breathing, respiratory neural drive and dyspnea

Typically, EILO develops during rigorous exercise and the degree of laryngeal closure is closely associated with exercise intensity (25). In the current study, discrete laryngeal movement started to occur in subjects with EILO at moderate to high exercise intensity (120–180W) and the de-facto threshold for significant obstruction (i.e. EILO sum score of >2 (19) or individual glottic or supra-glottic score of $\geq$2 (5, 13, 32)) was achieved in all subjects by 180W (Figure 2a). This discriminator was selected on the basis that scores of <2 are considered within a normal physiological response and consistent with the stress of heightened ventilation on laryngeal movement (19). Indeed some control subjects also developed a minor paradoxical laryngeal closure at peak exercise.

In keeping with the hypothesis that EILO represents a maladaptive response to exercise, the development of significant visual evidence of laryngeal closure was closely associated with a

significant increase in inspiratory resistive work of breathing with a proportionate increase in RND (Figure 2, Figure 3). Despite this there was however no difference in self-reported dyspnea intensity rating at high intensity exercise. Subjects with EILO tended to report less dyspnea at higher levels of $\dot{V}_E$ and RND (Figure 4), suggesting a potential perceptive adaptation to the increased work of breathing.

Individuals with EILO often report 'unsatisfied inspiration' or 'difficulty obtaining a satisfying breath' at high intensity. It is therefore of interest to note that the changes in RND observed are akin to those reported in *obstructive* lung conditions. We hypothesized that this increased work of breathing might contribute to exercise limitation (33), however no such limitation was evident in the present study; i.e. subjects with EILO and controls achieved similar peak work rates. In subjects with EILO, laryngeal closure usually develops during intense exercise (25); thus our findings highlight the importance of employing high intensity, constant work rate testing in future work.

Ventilatory response to exercise

An unexpected finding was evidence of greater minute ventilation, driven by augmented tidal volume excursion, in subjects with EILO when compared with controls. This difference was apparent from the early stages of exercise (i.e. 60W) and appeared to precede visual evidence of laryngeal closure (i.e. <2 on the grade scoring system for EILO (19)). Subjects who had developed EILO reached a critical inspiratory reserve volume at a lower work rate than controls, and started to increase their breathing frequency, thus maintaining a greater $\dot{V}_E$ than controls. This ventilatory pattern is consistent with increased static airway resistance as seen in simulated mild and moderate airway stenosis (33). Yet, at the early stages of exercise there was no evident laryngeal obstruction; thus laryngeal closure, as classified by a visual scoring system

at least, does not explain the observed difference in ventilatory pattern. This acknowledged, although not statistically significant, inspiratory resistive work of breathing and RND did appear to increase in the EILO group at low work rates (i.e. starting at 100W), coinciding with these ventilatory differences and a discrete and non-significant difference in dyspnea (Figure 4). Thus it may be that the physiological abnormalities observed provide a more precise and detailed insight regarding the consequences of flow impairment and potentially the development of turbulence at the laryngeal inlet than closure quantified by a relatively crude 2D visual recording perspective.

We suggest this admits two possible hypotheses with regard to underlying physiological mechanisms. The first is that subjects with EILO adopt a breathing pattern with an increased tidal volume because they have a high airway resistance, not just during vigorous exercise but also at light exercise and possibly at rest. The cause for this could be anatomical differences (e.g. genetically determined anatomical proportions of the airways) or microstructural changes (e.g. connective tissue defects that could alter the structural properties of the airways, increasing tissue compliance and the propensity to collapse). With this conjecture, at higher airflows, the larynx proportions or the laxity of the airway mucosa also causes laryngeal collapse, amplifying the problem by further increasing airway resistance at the level of the larynx.

Alternatively, it could be hypothesized that subjects with EILO have a breathing pattern with an unusually high tidal volume, maybe due to an over-expression of the adaptive response to maintain ventilation or as a consequence of an abnormal metabolic response. We did not measure lactate in the current study and this would be informative in future work, in this respect however, the increased and abnormal ventilation in itself causes the collapse of

laryngeal structures at high exercise intensity due to the Venturi effect, or as an adaptive measure to modulate carbon dioxide control (34). Not having performed full body plethysmography we unfortunately cannot determine whether this increased tidal volume and the differences in Cdyn at rest and lower work rates relate to decreased end-expiratory lung volume (12). However, we did not see any differences in surrogate markers of expiratory ventilatory muscle recruitment, or to a decreased inspiratory reserve volume in subjects with EILO. The underlying cause of this breathing pattern could be a central modulation of breathing, or could be caused by abnormalities of sensory input for example a sensory neuropathy that failed to allow the brain to correctly gauge rib cage expansion.

Critique of the method

The sample size in the present study was necessarily small, given the complex and invasive nature of the measurements. In addition, this has never before been made simultaneously and despite the small number of participants we were able to detect key physiological differences between the groups. It would have been attractive to study more participants and to examine changes in laryngeal behavior following an alternative hyperpnoeic stimulus (for example hypercapnia). Certainly, in future studies it would be desirable to obtain metabolic data (i.e. exhaled O_2 and CO_2) and blood gasses to provide insight regarding the ventilatory response in EILO. Moreover, a more detailed interrogation of dyspnea perception and other sensory responses (1, 29) would be valuable in future studies investigating how these symptoms relate to the development of EILO and changes in the physiological correlates. The impact of obstructive airflow on ventilatory loading and RND is now well described (26). Two subjects with EILO also had well-controlled mild asthma; however on the day of testing their symptoms were very well controlled and they had no evidence of airflow obstruction on spirometric testing. We therefore feel that it is unlikely that asthma influenced the reported findings.

In summary, for the first time, we identified that exercise-induced laryngeal closure is associated with objective physiological respiratory derangement (i.e. increased work of breathing and respiratory neural drive), and that ventilation is increased before this observable laryngeal closure occurs. These findings progress our physiological understanding of the sequelae of upper airway closure on the respiratory system. The methodology herein presented also presents a valid model to potentially study interventions (e.g. laryngeal surgery (18, 21, 24), speech- and language therapy (27) or anti-cholinergic inhaled therapy (7)), quantifying their impact with objective parameters.

CONCLUSION

Synchronized measurements of diaphragmatic electromyography and respiratory pressures with endoscopic video we demonstrate that respiratory work of breathing and respiratory neural drive increase in close association with the development of EILO. These findings highlight how upper airway closure contributes to respiratory derangement in EILO, and prompt need for further detailed investigations of the physiological mechanisms underpinning exertional dyspnea and exercise limitation in EILO.

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FIGURE LEGENDS

Figure 1: *Pictorial example of synchronized data collection in a subject with severe EILO and a matched control, exercising at 200W demonstrating (A) measurements of tidal airflow, esophageal pressure (Pes) and diaphragm electromyographic recordings (EMGdi); (B) laryngoscopic images at mid-inspiration and mid-expiration, depicting almost complete obstruction in the EILO subject on inspiration but not on expiration; (C) Campbell-diagrams of average pressure-volume loops illustrating increased work of breathing in the EILO subject. Dark gray area: inspiratory resistive work; light gray area: inspiratory elastic work; hatched area: total expiratory work. EILO: Exercise-induced laryngeal obstruction.*

Figure 2: *Exercise airway response expressed as EILO sum score i.e. glottic + supraglottic grade score (A), ventilation and breathing pattern response to exercise (B–F); EILO: Exercise-induced laryngeal obstruction.* T_i/T_{tot}*: Inspiratory duty cycle. The dashed vertical line shows the point at which all subjects with EILO had moderate or severe EILO visualized on the laryngoscopic recordings. Dotted lines illustrate that one or two subjects within the group did not reach this workload during the test.*

Figure 3: *Exercise respiratory neural drive (A), work of breathing (B–C), inspiratory flow at mid-volume,(D) and respiratory mechanics (E–F). EILO: Exercise-induced laryngeal obstruction. EMGdi: Diaphragm electromyogram. WOB: work of breathing. Pes: esophageal pressure. Pdi: Transdiaphragmatic pressure. Cdyn: dynamic compliance. The dashed vertical line shows the point at which all subjects with EILO had moderate or severe EILO visualized on the laryngoscopic recordings. Dotted lines illustrate that one or two subjects within the group did not reach this workload during the test.*

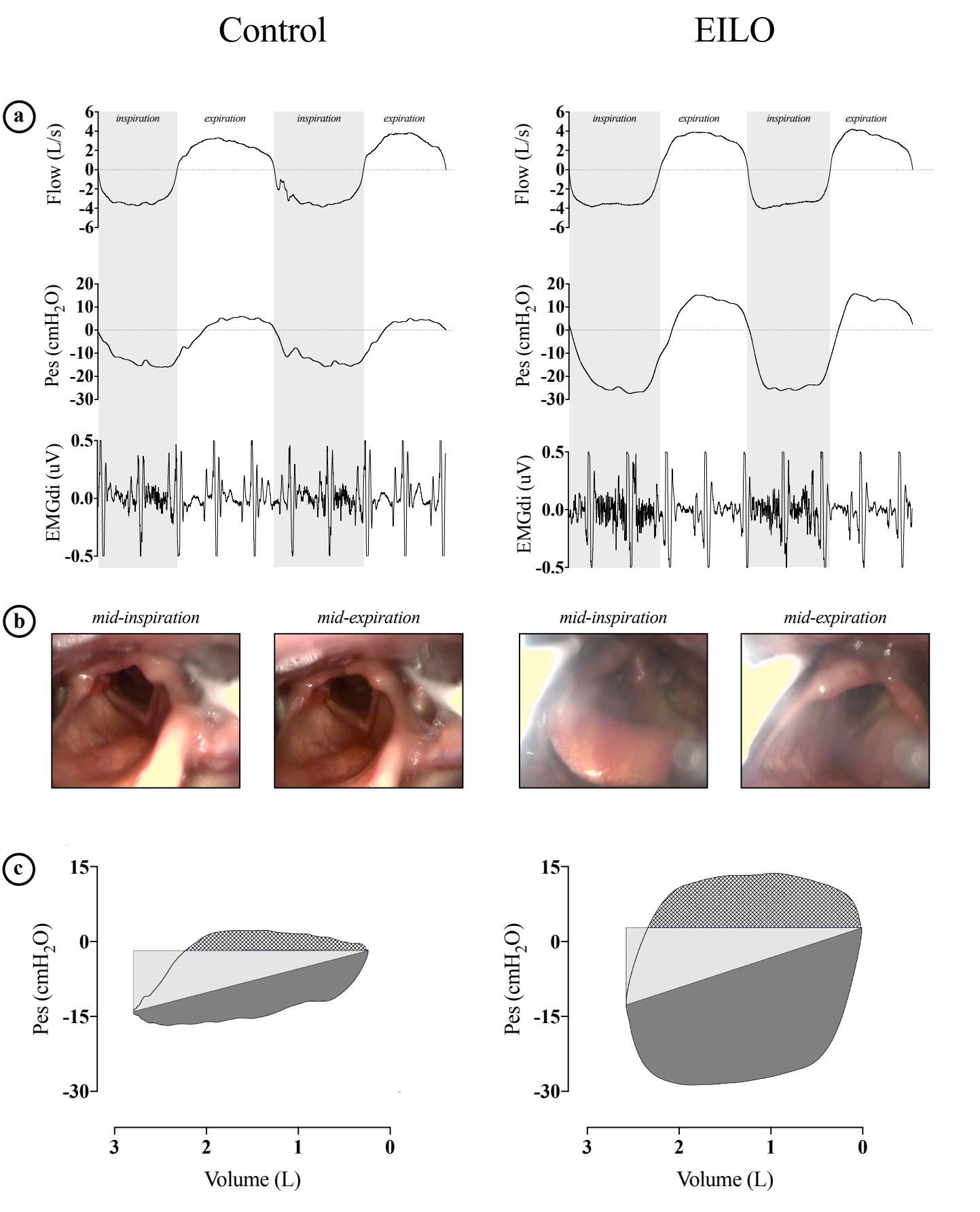
Figure 4**:** *Reported dyspnea intensity on the Borg CR10 scale as a function of work rate (A), ventilation (B) and neural respiratory drive (C). EILO: Exercise-induced laryngeal obstruction. EMGdi: Crural diaphragm electromyography. The dashed vertical line shows the point at which all subjects with EILO had moderate or severe EILO visualized on the laryngoscopic recordings. Dotted lines illustrate that one or two subjects within the group did not reach this workload during the test.*

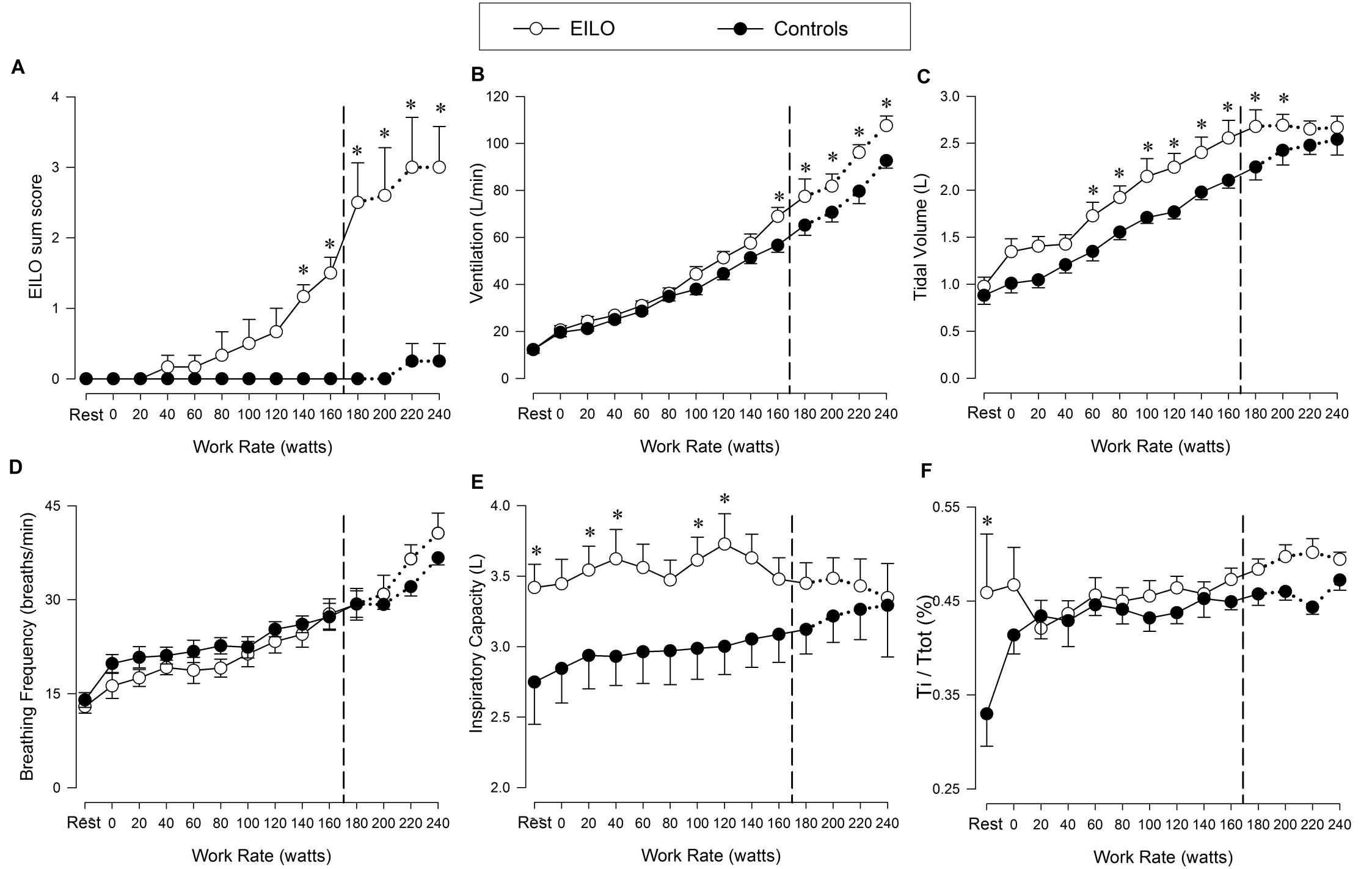
TABLES

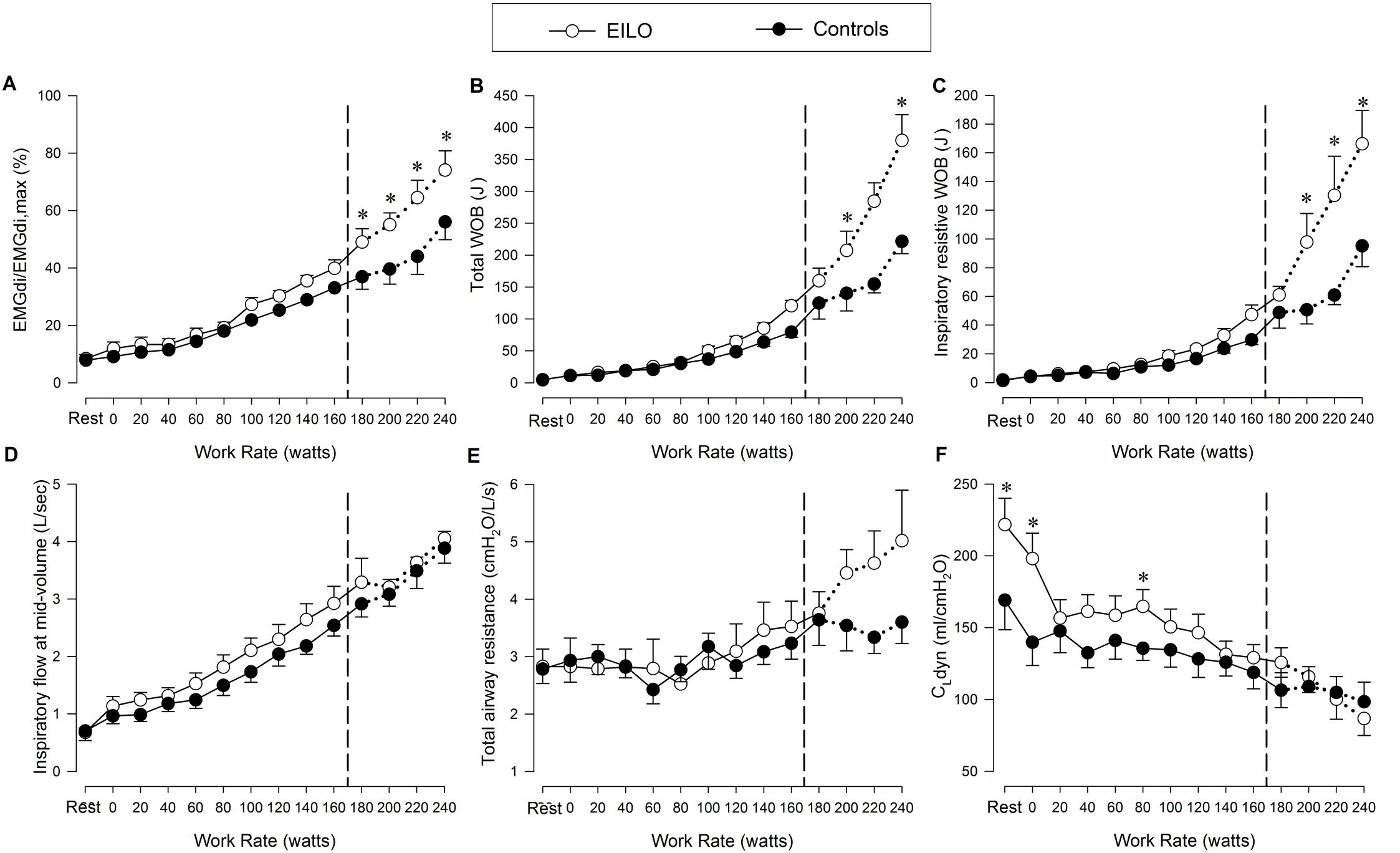
Table 1: Subject characteristics

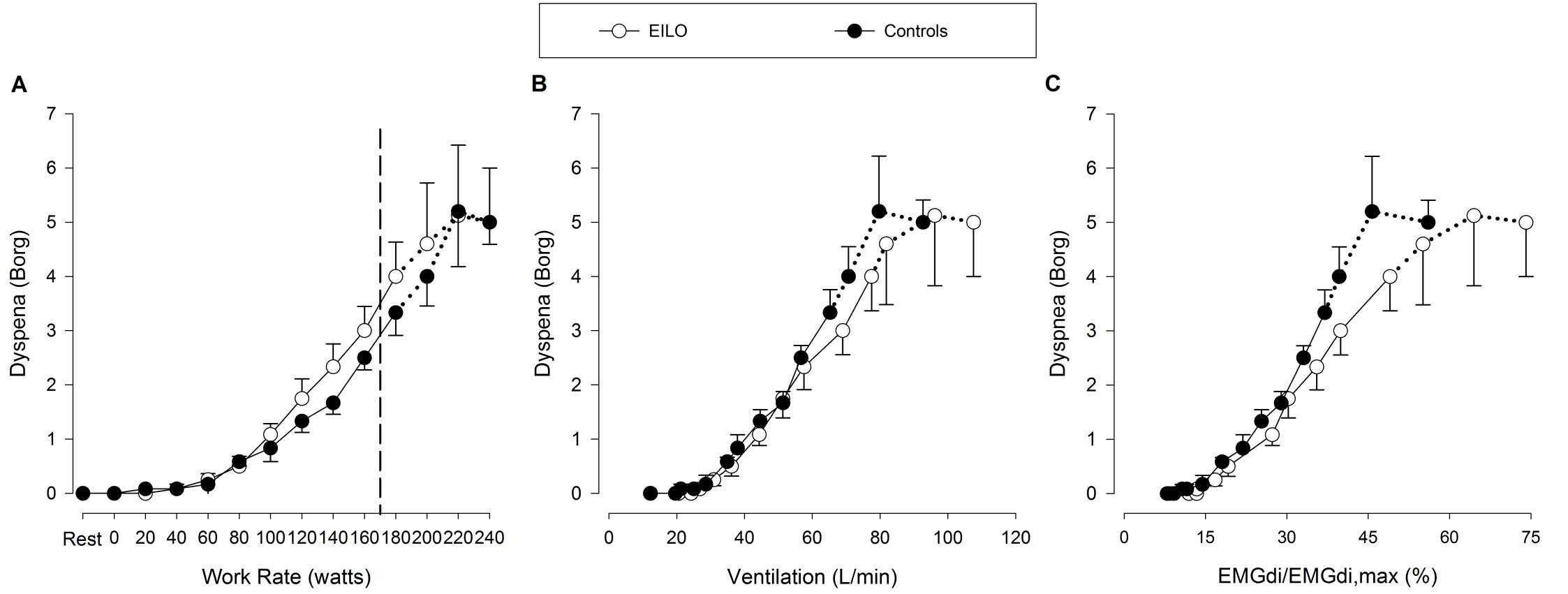
	Controls (n=6) *(5 females, 1 male)*			EILO (n=6) *(5 females, 1 male)*			
	Mean	***Median***	***(range)***	***Mean***	***Median***	***(range)***	***p***
Demographics							
Age, years	31	30	(27–38)	34	31	(28–44)	*0.32*
Height, cm	174	173	(167–183)	172	171	(166–179)	*0.59*
Weight, kg	70.7	74.0	(54.0–83.0)	68.0	67.2	(59.7–77.5)	*0.59*
Lung function							
PIF, L	8.06	8.01	(6.86–10.33)	6.70	6.34	(4.55–10.47)	*0.08*
FEV_1, L	3.82	3.66	(3.24–4.51)	3.86	3.65	(3.23–5.03)	*0.82*
FEV_1, % predicted	106.4	107.8	(93.9–115.2)	111.5	111.0	(98.7–131)	*0.49*
FVC, L	4.79	4.64	(4.25–5.65)	4.74	4.50	(4.09–5.76)	*0.70*
FVC, % predicted	115.5	118.0	(104.8–123.0)	120.3	119.9	(104.2–134.7)	*0.59*
IC, L	2.75	2.64	(1.75–3.89)	3.42	3.48	(2.92–4.00)	*0.09*
IC, % predicted	101.3	102.3	(73.4–128.3)	130.9	129.4	(115.0–153.4)	***0.02****
Exercise and respiratory mechanics							
Peak work rate, Watt	237	240	(180–280)	227	230	(180–280)	*0.66*
Peak work rate, % predicted	133	126	(110–161)	141	149	(135–189)	*0.82*
Pes (max, sniff)	87.1	89.9	(61.6–102.4)	76.3	76.4	(43.1–105.7)	*0.49*
Pes (max, IC)	63.5	58.1	(44.6–89.3)	52.1	54.1	(25.9–72.2)	*0.49*
Pes (max, MIP)	104.2	98.5	(75.5–147.3)	99.7	97.9	(39.8–162.2)	*0.82*
Pdi (max, sniff)	112.7	113.5	(72.6–150.9)	112.2	108.1	(82.0–167.5)	*0.94*
Pdi (max, IC)	86.5	87.3	(62.1–116.7)	73.7	71.8	(47.5–99.9)	*0.49*
Pdi (max, MIP)	148.6	142.3	(87.2–202.3)	137.5	132.2	(88.5–199.8)	*0.70*
Peak $\dot{V}_E$, L	98.1	88.4	(74.8–138.4)	103.2	108.3	(65.5–121.6)	*0.59*
Peak EMGdi, % max	60.0	59.5	(52.4–68.1)	67.7	65.8	(53.8–81.3)	*0.24*
Peak EMGdi, µV	259.3	262.4	(176.0–333.0)	229.9	223.6	(178.9–293.2)	*0.49*

Controls versus EILO p-values: Mann-Whitney U tests for continuous variables and Fisher's Exact for categorical variables; EILO: Exercise-induced laryngeal obstruction; PIF: Peak inspiratory flow. FEV_1: Forced expiratory volume in one second; Pes: esophageal pressure; Pdi: transdiaphragmatic pressure; FVC: Forced vital capacity; IC: Inspiratory Capacity; MIP: Maximal Inspiratory Pressure; $\dot{V}_E$: Minute ventilation; EMGdi: diaphragm electromyography.


Control
EILO
a
inspiration
expiration
inspiration
expiration
Flow (L/s)
6
4
2
0
-2
-4
-6
Pes (cmH2O)
20
10
0
-10
-20
-30
EMGdi (uV)
0.5
0.0
-0.5
b
mid-inspiration
mid-expiration
mid-inspiration
mid-expiration
c
Pes (cmH2O)
15
0
-15
-30
3
2
1
0
Volume (L)


EILO
Controls
A
EILO sum score
Work Rate (watts)
B
Ventilation (L/min)
Work Rate (watts)
C
Tidal Volume (L)
Work Rate (watts)
D
Breathing Frequency (breaths/min)
Work Rate (watts)
E
Inspiratory Capacity (L)
Work Rate (watts)
F
Ti / Ttot (%)
Work Rate (watts)
Rest 0 20 40 60 80 100 120 140 160 180 200 220 240


EILO
Controls
A
EMGdi/EMGdi,max (%)
B
Total WOB (J)
C
Inspiratory resistive WOB (J)
D
Inspiratory flow at mid-volume (L/sec)
E
Total airway resistance (cmH2O/L/s)
F
CLdyn (ml/cmH2O)
Rest 0 20 40 60 80 100 120 140 160 180 200 220 240
Work Rate (watts)


EILO
Controls
A
B
C
Dyspena (Borg)
Dyspena (Borg)
Dyspnea (Borg)
Rest 0 20 40 60 80 100 120 140 160 180 200 220 240
Work Rate (watts)
0 20 40 60 80 100 120
Ventilation (L/min)
0 15 30 45 60 75
EMGdi/EMGdi,max (%)